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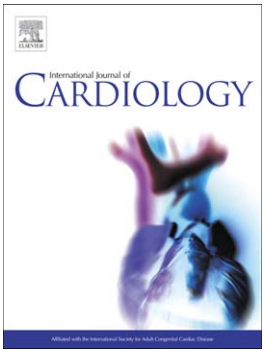

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The $CHADS_2$ and CHA_2DS_2-VASc scores for predicting ischemic stroke amongst East Asian patients with atrial fibrillation: A systemic review and meta-analysis

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ABSTRACT

BACKGROUND Both the $CHADS_2$ and CHA_2DS_2-VASc scores are well-validated in Western populations for predicting risk of stroke among patients with atrial fibrillation (AF). There is some uncertainty as to which risk score is best to guide optimal anticoagulant therapy among Asian populations with AF.

METHODS A systemic literature search of Cochrane library, Scopus, and PubMed databases was conducted using search terms: atrial fibrillation, $CHADS_2$ and CHA_2DS_2-VASc. Stroke/thromboembolism (TE) outcome events at low, moderate, and high risk groups were compared in relation to both scores. Statistical analyses were performed using Revman5.3 software.

RESULTS 493 records were retrieved, of which 6 cohort studies focusing on patients from Asian regions were finally appraised and included. Absolute event rates were usually lower when patients were categorized as CHA_2DS_2-VASc of 0-1, rather than $CHADS_2$ of 0-1, respectively. Meta-analysis revealed that when compared with the CHA_2DS_2-VASc score, there was a 1.71-fold elevated risk of stroke when patients were stratified as 'low risk' using a $CHADS_2$ score=0, or a 1.40-fold increase with a $CHADS_2$ score=1. A 1.19-fold elevated event rate was observed amongst $CHADS_2$ score ≥2 compared to CHA_2DS_2-VASc, but the total stroke/TE events were numerically higher in patients categorized as CHA_2DS_2-VASc ≥2.

CONCLUSION The CHA_2DS_2-VASc score is superior to the $CHADS_2$ score in identifying 'low risk' East Asian AF patients. Rather than a categorical approach,

Asian guidelines should adopt a 2 step approach, by initially identifying the truly low risk patients, following which effective stroke prevention can be offered to those with ≥1 additional stroke risk factors.

KEYWORDS: Atrial Fibrillation; CHA_2DS_2-VASc; $CHADS_2$; Asia

1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia conferring an increased risk of stroke and thromboembolism (TE), and patients with AF-related stroke have an even worse prognosis than patients without AF, with longer hospitalizations, more disability and higher in-hospital mortality [1]. Despite a five-fold increased risk of stroke overall among AF patients, this risk is heterogeneous, depending on the presence and absence of several stroke risk factors.

Given the need for estimating the risk of stroke/TE, clinical risk stratification schemes have been recommended to assist the clinician in selecting optimal thromboprophylaxis for appropriate individuals. The $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke) score which was initially derived from amalgamation of the Atrial Fibrillation Investigators' and Stroke Prevention in Atrial Fibrillation Investigators' Schema[2], is recommended in the American College of Chest Physicians (ACCP) and Canadian Cardiovascular Society guidelines[3, 4]. The recently proposed CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category [female]) score is now recommended by the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS), European Society of

cardiology (ESC), and National Institute for Health and Care Excellence (NICE)[5-7]. However, most validation studies have been in Western populations, and some uncertainty is evident for the selection of which score to guide optimal anticoagulant therapy among Asian populations with AF [8]. Thus, many clinicians in Asian countries prefer to the older $CHADS_2$ score, which is perceived to be simple and easy to use.

Nonetheless, it has been recognized that even patients categorized as low-risk by a $CHADS_2$ of 0 are not necessarily at low risk of stroke, and the CHA_2DS_2-VASc score is often best to identify patients at "truly low risk" of stroke/TE [9, 10].

Given the uncertainty over which score is best in Asian patients with AF, our objective was to perform a systemic review and meta-analysis of available studies to compare $CHADS_2$ and CHA_2DS_2-VASc scores for risk stratification and second, to establish if which score has a better performance in identifying 'truly low risk' Asian patients with AF.

2. Methods

Inclusion and Exclusion Criteria

The following inclusion criteria were used for study selection: 1) *Types of studies:* randomized controlled trials (RCT) or observational cohort studies focusing on the $CHADS_2$ and CHA_2DS_2-VASc scores for predicting the risk of stroke/TE; 2) *Types of participants:* AF patients from East Asian regions, including China, Taiwan, Japan, Korea; 3) *Types of Interventions:* No anticoagulation therapy; 4) *Types of outcome measures:* primary endpoints of ischemic stroke, TE, or both. Exclusion criteria were as follows: 1) Duplicated report on a same cohort; 2) Certain publication types, such as conference abstracts, letters, comments, case reports, and editorials [as we wished to focus on peer reviewed, robust *published* data]; 3) Studies not published in English. 4) Data presented for a population from regions outside East Asia, or the original source of study was not specified. 5) Study population of <300 people, and the mean follow-up duration < 1 year [This was to avoid use of underpowered data].

2.1 Literature Search

Comprehensive literature searches were undertaken using Cochrane library, PubMed and Scopus databases for studies published between January 1, 2010 and March 1, 2015, in view of the first research on CHA_2DS_2-VASc being published in 2010. Search terms included "atrial fibrillation", "$CHADS_2$" and

"CHA_2DS_2-VASc". The electronic search was carried out for peer-reviewed journals, and some further additional data not identified in the electronic database were collected from other data resources, especially some original data was absent in the published articles. Specifically, we contacted with the corresponding authors to get the original data not reported in the published articles.

2.2 Data Extraction

All literature retrieved by the search strategy were screened by two reviewers (QX and SC) independently. The first sift-prescreening was performed by reading titles and abstracts to select studies for further data extraction. The second sift-selection was undertaken by comprehensively reviewing the full text to check if they reported the stroke/TE event rates or number at each points of $CHADS_2$ and CHA_2DS_2-VASc scores, and the original region of participants. Articles meeting the eligibility criteria were selected after review of full text.

Data were extracted from each eligible study or calculated from the data presented, including the baseline characteristics of participants, follow-up duration, stroke/TE event rates or number for each point of both scoring system. Study endpoints, for example, ischaemic stroke, was taken as that defined in respective individual studies. If the event number was unavailable in the full text or by contacting the corresponding authors, it was calculated by using the

following formula: Event number = (Total patient number) x (Event rate [per 100 patient years]) x (Follow-up duration [years]). Discrepancies were resolved by consensus or, if necessary, through discussion or consultation with a third reviewer (KS).

2.3 Quality Assessment and risk of bias

Newcastle-Ottawa Scale were used for assessing the quality of all included cohort studies in this meta-analysis, involving selection of cohorts, comparability of cohorts, and assessment of outcome[11]. Both risk of bias and quality of included studies were evaluated by two reviewers (QX and SC) independently.

2.4 Statistical Analysis

Statistical analyses were performed using Review Manager Version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Scores of 0, 1 and ≥ 2 were defined as the low, moderate, and high risk categories, respectively, for each scoring system. Stroke/TE events were measured as dichotomous outcome variables, compared between the same risk categories according to $CHADS_2$ and CHA_2DS_2-VASc scores. Relative risk (RR) was calculated and presented with 95% confidence interval (CI) for the summary estimates. In view of the heterogeneity between included studies, appropriate statistical models, fixed-effect or random-effect models, were selected to ensure that the various statistics were estimated correctly. Cochran's chi-square test and I^2

statistic were measured to evaluate the heterogeneity between included studies. Cochran's chi-square test was used to find out whether the observed difference may be due to chance alone. A low P-value means significant heterogeneous results among different study, with a cut-off at 0.10. The I^2 statistic can describe the percentage of total variation across the studies that are due to significant heterogeneity rather than random chance. If I^2 statistic is higher than 75%, it suggests that there is considerable heterogeneity among these studies. The correction for publication bias was assessed by funnel plot analyses. Statistical significance was set at a P-value < 0.05.

3. Results

A total of 493 records were identified through above mentioned literature search strategy. After removing duplicates, we extracted 238 records for screening. Following this, 201 were excluded by reviewing title or abstract and full texts of the remaining 37 articles were retrieved for further review if they met the predetermined criteria. Finally, six eligible studies were identified and included in the present meta-analysis [12-17]. The literature search flow diagram is shown in Figure 1.

3.1 Study Characteristics

Patient characteristics from each included study were shown in Table 1. In the present study, data from 31539 AF patients (15271 females, 48.4%) were pooled for further analyses. Among these studies, two population cohorts were from Taiwan nationwide database, focusing on non-valvular AF patients [15], and AF patients with end-stage renal dysfunction (ESRD) [12], respectively. In the Japanese study of Suzuki et al., data were pooled from Shinken Database, J-RHYTHM Registry, and Fushimi AF Registry to identify the ischemic stroke rates in Japanese non-valvular AF patients without anticoagulant therapy[17].

3.2 Event rates

The total event rates of ischemic stroke/TE varied from 2.10 to 9.28 per 100

person-years in non-anticoagulated AF patients from different observational cohorts (Table 1). Event rates at different points of the $CHADS_2$ and CHA_2DS_2-VASc scores are shown in Figure 2.

In the Taiwan nationwide cohort enrolling AF patients with ESRD, the overall incidences of stroke /TE were higher on the basis of both scores, compared with those observed in other cohorts[12]. In the cohort of Japanese non-valvular paroxysmal AF patients who were not receiving anticoagulation therapy, the event rates were even higher at $CHADS_2$ of 3, ≥4, and CHA_2DS_2-VASc of 5, ≥6 [14]. In the low risk category of three included studies, event rates based on CHA_2DS_2-VASc score were lower, compared those based on $CHADS_2$ score. All event rates in the moderate risk category were lower on the basis of CHA_2DS_2-VASc score, as shown in Figure 2.

3.3 Quality Assessment

Assessment of the quality of all included studies was undertaken using NOS items designed for cohort studies. These studies were of high quality presented with 8 or 9 stars, as shown in Table 3. Three papers [12, 14, 17] received three stars in the selection items due to pooled analysis or selecting particular AF patients such as paroxysmal AF patients and AF patients with ESRD. A possible absence of publication bias was observed using a funnel plot (Figure 3).

3.4 Data synthesis

(a) Low risk category

In a pooled analysis of all included patients at low risk of ischemic stroke/TE, a very low heterogeneity was observed, as reflected by I^2 statistic of 10%, indicating that the variability between these studies was acceptable. Among all included AF patients, there were 4942 patients considered at very low risk with a $CHADS_2$ score of 0, but 259 (5.2%) experienced ischemic stroke/TE events during follow-up. In 1774 patients with CHA_2DS_2-VASc score of 0, only 45 (2.5%) had ischemic stroke/TE events during follow-up. When data were pooled across these studies, low risk patients with $CHADS_2$ score of 0 had a significant higher risk of ischemic stroke/TE endpoints compared to those 'low risk' patients defined with a CHA_2DS_2-VASc score of 0 (RR, 1.71; 95%CI: 1.26-2.31), as shown in Figure 4.

(b) Moderate risk category

In the pooled analysis of patients with moderate risk of ischemic stroke/TE, there was no heterogeneity between these included studies in view of the I^2 statistic of 0%, indicating that all these studies were comparable when we performed this pooled analysis. Among 7449 AF patients with $CHADS_2$ score of 1, 689 (9.2%) experienced ischemic stroke/TE during observation period, compared to 171 (5.2%) of 3281 AF patients categorized as CHA_2DS_2-VASc score of 1. The risk of ischemic stroke/TE risk was higher when patients were

stratified with $CHADS_2$ score of 1, compared with when categorized by a CHA_2DS_2-VASc score of 1 (RR, 1.40; 95%CI: 1.20-1.64), as shown in Figure 5.

(c) High risk category

When comparing the incidence of events in the high risk category on the basis of both scores, high heterogeneity was observed, with an I^2 statistic of 83%. Therefore, a random effects model was selected to carry out the pooled analysis, and the results should be interpreted cautiously.

When CHA_2DS_2-VASc score ≥2 was used to identify patients at high risk of ischemic stroke/TE, there were more patients (n=3387; 12.7%) experiencing events during follow-up. The pooled analysis found a higher risk of ischemic stroke/TE in patients with $CHADS_2$ score ≥2 (RR, 1.19; 95%CI: 1.02-1.38), but the total number of stroke/TE events and rates were higher among all included patients when categorized as CHA_2DS_2-VASc score ≥2.

4. Discussion

In this systematic review and meta-analysis, our principal finding was that event rates of ischemic stroke/TE were usually lower in patients categorized as low-moderate risk by use of the CHA_2DS_2-VASc score, when compared with those based on $CHADS_2$ score. Second, the pooled analysis indicated that CHA_2DS_2-VASc score was particularly helpful to identify AF patients at low-risk among Asian populations. Thus, those patients with $CHADS_2$ score of 0 or 1 should be further stratified using CHA_2DS_2-VASc score for predicting stroke/TE risk.

4.1 Event rates

The differences in ischemic stroke/TE event rates between included studies reflect the different patient cohorts and the details of methodology, such as the length of follow-up and the intervention of participants. For example, Chao et al. included AF patients with ESRD requiring dialysis, and the event rates were even higher at each point compared to other cohorts[12]. Despite this, all included studies were homogenous for the comparison of ischemic stroke/TE events in low-moderate categories between both scores, as reflected by low I^2 statistics of 0% and 10%.

The overall ischemic stroke/TE rates in non-anticoagulated AF patients from Asian countries, ranged from 2.10 to 9.28 per 100 person-years, were

comparable to (or even higher than) corresponding rates published for Caucasians. Indeed, the reported rate of AF-related stroke was similar at 13.0% to 15.4% in community-based cohort studies from China, Japan, Singapore, and Taiwan[18].

4.2 $CHADS_2$ versus CHA_2DS_2-VASc score

Both $CHADS_2$ and CHA_2DS_2-VASc scores are useful risk stratification tools for predicting ischemic stroke/TE. More recently, the CHA_2DS_2-VASc score has been shown to have a better performance, as presented by higher C-statistics in several cohort studies [12, 13, 16, 19, 20]. A previous meta-analysis demonstrates an approximately 6-fold increased risk of stroke/TE in AF patients with CHA_2DS_2-VASc of ≥2, which was significantly better than the 3-fold increased risk predicted by a $CHADS_2$ score of ≥2[21]. However, no significant difference in predictive ability between both scores has been found in one Japanese cohort study [14]. Due to the traditional belief of a higher bleeding risk but lower stroke risk among Asian populations, the $CHADS_2$ score, but not the CHA_2DS_2-VASc score is widely recommended by AF guidelines or expert consensus in many Asian countries, such as Japan. In the APHRS guidelines, the CHA_2DS_2-VASc score is the recommended risk scoring system [22].

Given that the risk profile of AF patients is not static but a dynamic one, a potential bias on the incidence of ischemic stroke/TE will be introduced when

the methodology of study differs. As demonstrated in the Taiwanese cohort, even patients with $CHADS_2$ of 0 or 1 can have CHA_2DS_2-VASc scores ranging from 0 to 4, with an increasing incidence of ischemic stroke from 2.1 to 4.7 per 100 person-years[12]. This is consistent with the results from the Danish nationwide cohort study, which has shown that patients with $CHADS_2$ of 0 can be subdivided by CHA_2DS_2-VASc scores into 0 to 4, with stroke/TE rates from 0.84 to 3.2 per 100 person-years at one-year follow-up[9]. Another study reported that among AF patients who had indication for anticoagulation by CHA_2DS_2-VASc score but categorized as "not for anticoagulation" using the Canadian Cardiovascular Society algorithm based on the $CHADS_2$ score, the overall incidence of ischemic stroke/TE was 4.32 per 100 person-years[23]. In view of these findings, patients with $CHADS_2$ score of 0 are not necessarily at "low risk" for the development of a potentially fatal or disabling stroke.

The present analysis shows that similar to other European cohorts, the CHA_2DS_2-VASc score is useful in identifying truly low risk AF patients from the Asian population [20, 24-26]. This is further reinforced by another Taiwanese cohort study which demonstrated a better performance of CHA_2DS_2-VASc score for refining low risk Asian AF patients, comparing with another risk scoring system, the anticoagulation and risk factors in atrial fibrillation (ATRIA) score[10].

For patients with significant/high risk of stroke/TE, as predicted by CHA_2DS_2-VASc or $CHADS_2$ score of ≥2, decision making on recommending anticoagulation is easy regardless of which score should be used, as the therapeutic decision is similar (i.e. anticoagulation) whether the score is 2,3,4 or higher. For those patients with a $CHADS_2$ score of 0 or 1, efforts should be made to identify individuals who can potentially benefit from anticoagulation therapy. Thus, the focus should be drawn on the truly low-risk patients and those with one additional risk factor (CHA_2DS_2-VASc score of 1 in male, 2 in female), where anticoagulation is also likely to benefit [27, 28].

The present analysis clearly provides compelling evidence supporting use of the CHA_2DS_2-VASc score for stroke risk stratification in Asian patients with AF, given its refinement of identifying 'truly low risk' patients. Asian physicians have generally been unconvinced by the applicability of non-Asian data, which is why we need to specifically show that the CHA_2DS_2-VASc does work better in identifying low risk patients in the Asian populations.

Rather than a categorical (i.e. low/moderate/high risk) approach to stroke risk and treatment decisions, the ESC and NICE guidelines recommend a 2 step approach. The 1st step is to identify 'low risk' patients (CHA_2DS_2-VASc score of 0 in males, 1 in females) who do not need any antithrombotic therapy. The next step is to offer effective stroke prevention (which is oral anticoagulation) to those

with ≥1 additional stroke risk factors, irrespective of the CHA_2DS_2-VASc score value.

4.3 Limitations

Several limitations should be addressed in this present study. Firstly, limited eligible data can be available for this meta-analysis. We extracted only 6 cohort studies from China, Japan, and Taiwan, respectively. No data from other Asian countries can be included for pooled analysis, such as Singapore, Malaysia, Korea, etc. Thus, our findings are not representative for the whole Asia. Second, a high heterogeneity was observed when comparing the ischemic stroke/TE events in high-risk patients between both groups. Nonetheless, this study particularly focuses on the predictive ability of low-moderate risk of ischemic stroke/TE among Asian AF patients. Finally, the 'truly low-risk' patients are a CHA_2DS_2-VASc score of 0 in male and 1 in female, with stroke event rates of 0.49 per 100 person-years at 1-year[28]. Nevertheless, given that all published data thus far make no similar definition, only patients with CHA_2DS_2-VASc score of 0 were stratified into the low risk category in the present meta-analysis. Further studies are warranted to identify 'truly low risk' patients based on a more detailed stratification for males and females.

5. Conclusion

In conclusion, the CHA_2DS_2-VASc score is superior to the $CHADS_2$ score in

identifying 'truly low risk' Asians patients with AF. Rather than a categorical (i.e. low/moderate/high risk) approach to stroke risk and treatment decisions, Asian guidelines should adopt a 2 step approach, by initially identifying the low risk patients (using the CHA_2DS_2-VASc score) who do not need any thromboprophylaxis, following which effective stroke prevention can be offered to those with ≥1 stroke risk factors.

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Figure 1. Study Search Diagram

Figure 2. Event rates of ischemic stroke/TE at each point based on $CHADS_2$ and CHA_2DS_2-VASc scores

Figure 3. Funnel plot shows all studies included in the bias analysis.

Figure 4.
Comparison of ischemic stroke/TE events in the low risk category on the basis of $CHADS_2$ and CHA_2DS_2-VASc scores

Figure 5.
Comparison of ischemic stroke/TE events in the moderate risk category on the basis of $CHADS_2$ and CHA_2DS_2-VASc scores

Figure 6.
Comparison of ischemic stroke/TE events in the high risk category on the basis of $CHADS_2$ and CHA_2DS_2-VASc score

Table 1. Patient characteristics in the included studies

Study ID	Data source	Study cohort	Follow-up	Patients Number*(n)	Female (%)	Age (years)	Outcome of interest	Total event rate (number)
Chao, TF 2014[12]	Taiwan (Jan 1996-Dec 2011)	AF with ESRD	13m (median)	10,999	53.8	71.0±11.1	Ischemic stroke	6.9 (1,217)
Guo, YT 2013 [13]	China (Beijing, Nov2007-Jul 2010)	AF	1.9y (median)	885	26.6	75 (63-83)	TE	3.7 (NA)
Komatsu, T 2014 [14]	Japan (Jun 1995-Aug 2008)	Paroxysmal NVAF	53m (mean)	332	32.5	65±13	Ischemic stroke/TE	2.1 (NA)
Lin, YL 2011 [15]	Taiwan (1997-2008)	NVAF	1637d (median)	7,920	45.9	≥20#	Ischemic stroke	0.35-6.52¶ (NA)
Siu, CW 2014 [16]	China (Hong Kong Jul 1997-Dec 2011)	NVAF	3.19 (mean)	7,815	53.2	76.9±12.5	Ischemic stroke	9.28 (1795)
Suzuki, S 2015 [17]	Japan (Shinken, J-Rhythm, Fushimi)	NVAF	NA	3,588®	33.9	68.1±13.5	Ischemic stroke	0.35-7.24¶ (69)

AF = Atrial fibrillation; NVAF = Non-valvular AF; ESRD = End stage of renal dysfunction; TE = Thromboembolism; NA = not available

*Number of patients without anticoagulant therapy

The percentages of patients aged 20-64 yrs, 65-74 yrs, ≥75yrs were 36.7%, 30.9%, and 32.4%, respectively.

¶ The range of event rates at each point of $CHADS_2$ and CHA_2DS_2-VASc

®Data were pooled from the Shinken Database (n=1,099), J-RHYTHM Registry (n=1,002), and Fushimi AF Registry (n=1,487)

Table 2. Ischemic stroke/TE event rates at low/moderate risk category based on $CHADS_2$ and CHA_2DS_2-VASc scores

Study ID	Ischemic stroke/TE event rates (per 100 person-years)			
	$CHADS_2$=0	CHA2DS2-VASc=0	$CHADS_2$=1	CHA2DS2-VASc=1
Chao, TF 2014 [12]	2.0	2.1	3.5	2.4
Guo, YT 2013 [13]	0	0	2.9	0.9
Komatsu, T 2014 [14]	0.21	0	0.93	0.60
Lin, YL 2011 [15]	0.45	0.35	0.97	0.50
Suzuki, S 2015 [17]	0.54	0.53	0.93	0.55

Table 3. Quality assessment of all included studies

	Selection	Comparability	Outcome
Chao, TF 2014[12]	☆☆☆	☆☆	☆☆☆
Guo, YT 2013 [13]	☆☆☆☆	☆☆	☆☆☆
Komatsu, T 2014 [14]	☆☆☆	☆☆	☆☆☆
Lin, YL 2011 [15]	☆☆☆☆	☆☆	☆☆☆
Siu, CW 2014 [16]	☆☆☆☆	☆☆	☆☆☆
Suzuki, S 2015 [17]	☆☆☆	☆☆	☆☆☆

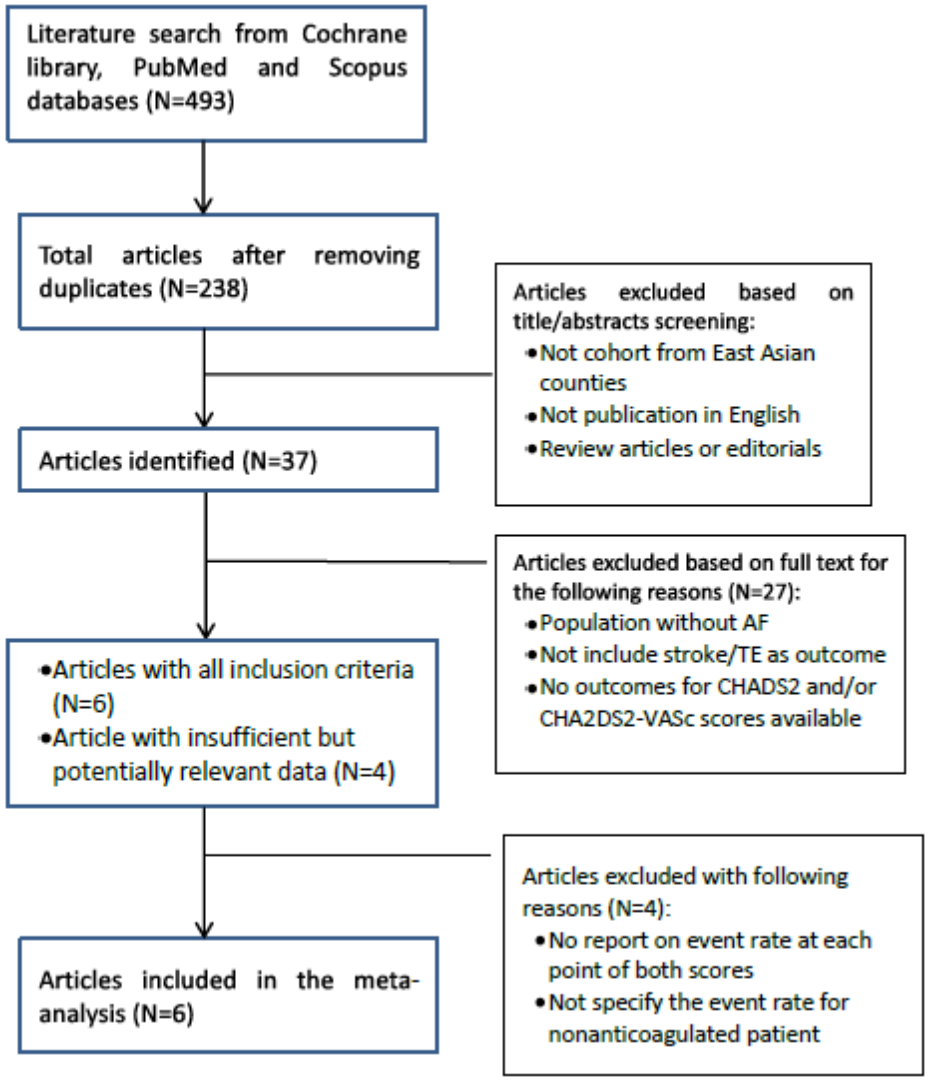

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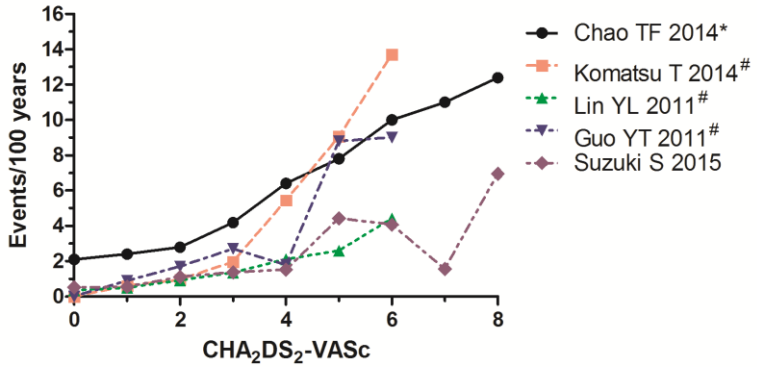
Fig. 1

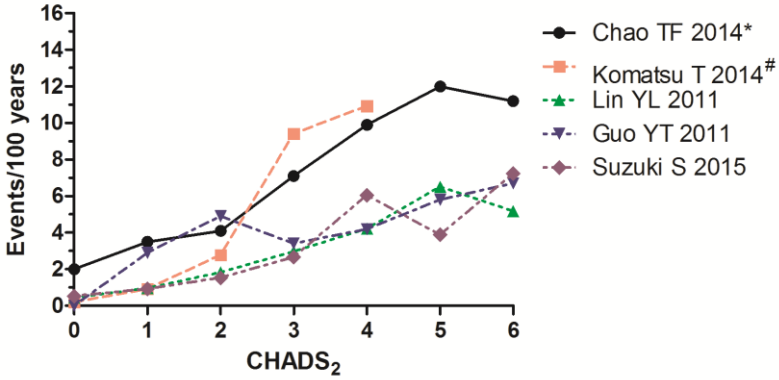
Event rates by CHA_2DS_2-VASc score



* This study cohort included AF patients with end stage renal dysfunction

Points at score 6 were event rates for patients with CHA_2DS_2-VASc ≥6

Event rates by $CHADS_2$ score



* This study cohort included AF patients with end stage renal dysfunction

Points at score 4 were event rates for patients with $CHADS_2$ ≥4

Fig. 2

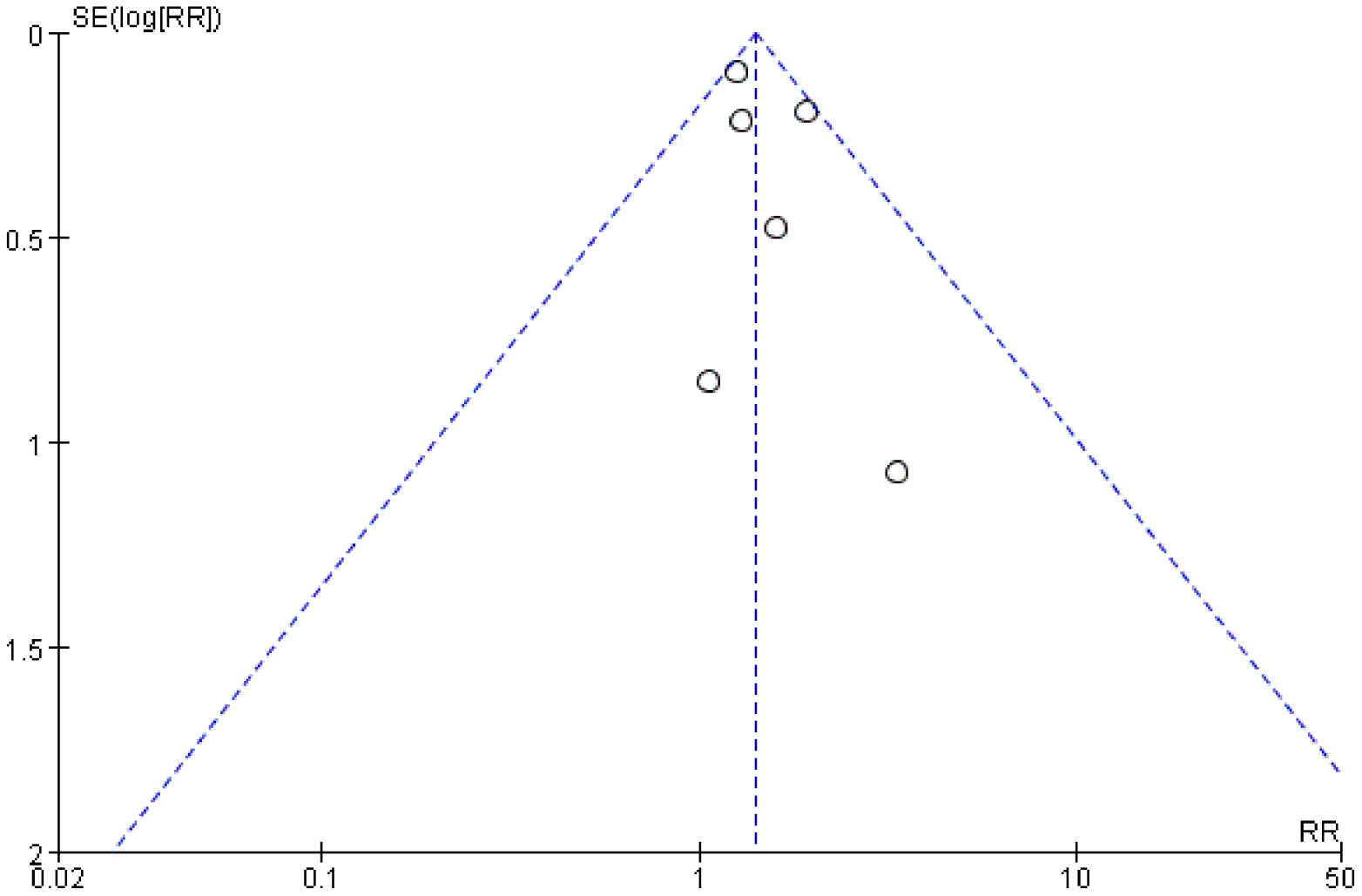


Fig. 3

Study or Subgroup	$CHADS_2$=0 Events	Total	CHA_2DS_2-VASc=0 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chao TF 2014	17	302	5	78	11.5%	0.88 [0.33, 2.31]
GuoYT 2013	0	88	0	52		Not estimable
Komatsu T 2014	1	115	0	76	0.9%	1.99 [0.08, 48.25]
Lin YL 2011	47	2335	10	659	22.5%	1.33 [0.67, 2.61]
Siu CW 2014	185	1012	25	292	56.0%	2.14 [1.44, 3.18]
Suzuki S 2015	9	1090	5	617	9.2%	1.02 [0.34, 3.03]
Total (95% CI)		**4942**		**1774**	**100.0%**	**1.71 [1.26, 2.31]**
Total events	259		45			

Heterogeneity: $Chi^2 = 4.45$, $df = 4$ ($P = 0.35$); $I^2 = 10\%$

Test for overall effect: $Z = 3.43$ ($P = 0.0006$)

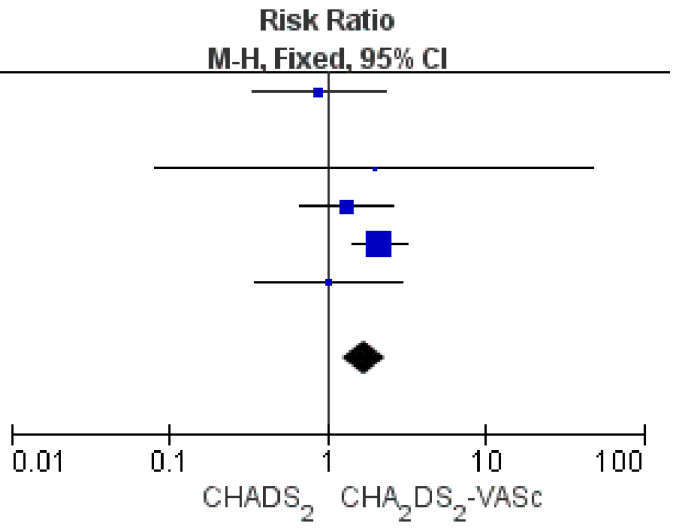


Fig. 4

Study or Subgroup	$CHADS_2$=1 Events	Total	CHA_2DS_2-VASc=1 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chao TF 2014	99	1107	24	348	14.4%	1.30 [0.84, 1.99]
GuoYT 2013	6	206	1	114	0.5%	3.32 [0.40, 27.24]
Komatsu T 2014	4	114	2	60	1.0%	1.05 [0.20, 5.58]
Lin YL 2011	126	2904	33	1467	17.3%	1.93 [1.32, 2.82]
Siu CW 2014	438	1949	105	590	63.7%	1.26 [1.04, 1.53]
Suzuki S 2015	16	1169	6	702	3.0%	1.60 [0.63, 4.07]
Total (95% CI)		**7449**		**3281**	**100.0%**	**1.40 [1.20, 1.64]**
Total events	689		171			

Heterogeneity: $Chi^2 = 4.83$, $df = 5$ ($P = 0.44$); $I^2 = 0\%$

Test for overall effect: $Z = 4.24$ ($P < 0.0001$)

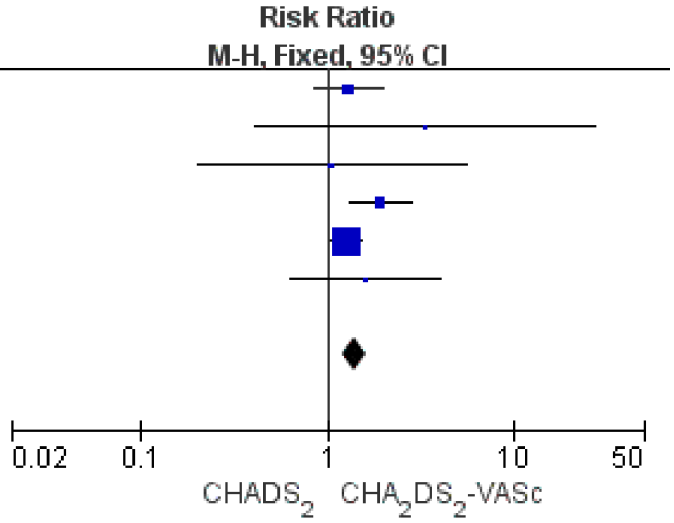


Fig. 5

Study or Subgroup	$CHADS_2$ ⩾2 Events	Total	CHA_2DS_2-VASc ⩾2 Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chao TF 2014	1101	9590	1188	10573	25.6%	1.02 [0.95, 1.10]
GuoYT 2013	27	591	32	719	7.1%	1.03 [0.62, 1.69]
Komatsu T 2014	32	103	35	196	9.2%	1.74 [1.15, 2.64]
Lin YL 2011	279	2681	409	5793	22.0%	1.47 [1.27, 1.70]
Siu CW 2014	1172	4854	1665	6933	26.1%	1.01 [0.94, 1.07]
Suzuki S 2015	44	1329	58	2269	10.1%	1.30 [0.88, 1.91]
Total (95% CI)		**19148**		**26483**	**100.0%**	**1.19 [1.02, 1.38]**
Total events	2655		3387			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 29.73$, $df = 5$ ($P < 0.0001$); $I^2 = 83\%$

Test for overall effect: $Z = 2.17$ ($P = 0.03$)

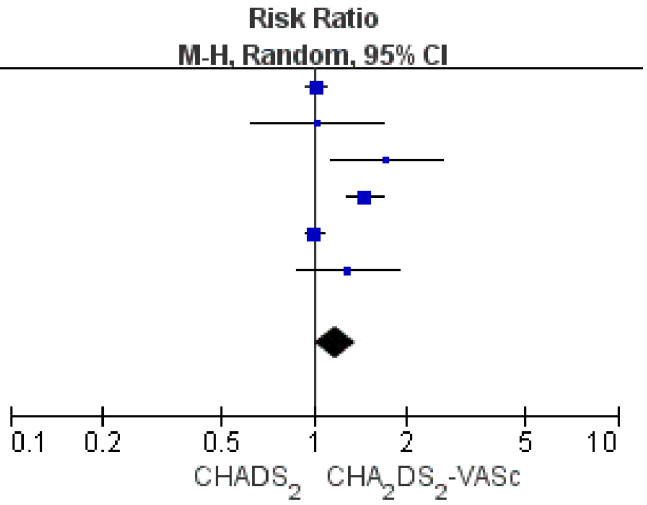


Fig. 6